This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (currently amended) A method for producing an antibody or antigen binding fragment in high yield from a host cell ~~cell culture~~, comprising:

a) expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified ~~FR~~ framework region (FR) in the ~~a~~ host cell, wherein

i) the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein

the at least one amino acid position and the different amino acid ~~is the~~ are determined by selecting a ~~amino acid found at the corresponding FR position of a~~ human subgroup variable domain consensus sequence that has a ~~HVR1~~ hypervariable region 1 (HVR1) and/or ~~HVR2~~ hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a ~~corresponding~~ HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of the corresponding position of the FR of the antibody or antigen binding fragment, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region; ~~, wherein~~

~~the antibody or antigen binding fragment variable domain comprising the modified FR has improved yield in cell culture compared to an unmodified antibody or antigen binding fragment;~~ and

b) recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR ~~framework~~ from the host cell.

2. (original) The method according to claim 1, wherein the antibody or antigen binding fragment is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a human antibody, a multispecific antibody, diabodies, or an antibody generated by phage display.

3. (currently amended) The method according to claim 2, wherein the antigen binding fragment is a Fab fragment, ~~F(ab')2~~ F(ab')$_2$ fragment, scFV fragment, or ~~sc(Fv)2~~ sc(Fv)$_2$ fragment, a single arm antibody or single chain antibody.

4. (currently amended) The method according to claim 1, wherein the antibody is an anti-VEGF antibody ~~or an anti-IgE antibody~~.

5. (previously presented) The method according to claim 4, wherein the antibody is a humanized antibody.

6. (previously presented) The method of claim 1, wherein expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell comprises expressing a polynucleotide encoding the variable domain comprising the at least one modified FR.

7. (original) The method of claim 6, wherein the polynucleotide further comprises a polynucleotide encoding a constant region domain connected to the polynucleotide encoding the variable domain with modified FR to form a polynucleotide encoding a full-length heavy or light chain.

8. (currently amended) The method of claim [[7]] 6, wherein the polynucleotide ~~further comprises~~ is comprised within an expression vector.

9. (previously presented) The method of claim 7, further comprising recovering a full-length heavy or light chain or both from the culture.

10. (previously presented) The method according to claim 1, wherein the host cell is a prokaryotic host cell.

11. (previously presented) The method according to claim 1, wherein the host cell is a mammalian cell.

12. (previously presented) The method according to claim 1, wherein the variable domain is a heavy chain variable domain or a light chain variable domain.

13. (currently amended) The method according to claim 12, wherein the HVR1 amino acid sequence of the variable domain of the antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14)[[,]] or GYDFTHYGMN (SEQ ID NO:18)~~, or GYSITSGYSWN (SEQ ID NO:19)~~.

14. (previously presented) The method according to claim 1, wherein the framework region is selected from the group consisting of FR1, FR2, FR3, FR4 and mixtures thereof.

15. (original) The method according to claim 14, wherein the human subgroup FR consensus sequence is a heavy chain FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

16. (previously presented) The method according to claim 1, wherein the yield of the antibody or antigen binding fragment comprising the modified FR is improved at least 2 fold compared to the unmodified antibody or antigen binding fragment.

17. (original) The method according to claim 16, wherein the yield of the antibody or antigen binding fragment comprising the modified FR is improved at least 2 fold to 16 fold compared to the unmodified antibody or antigen binding fragment.

18. (currently amended) The method of claim 1, wherein at least two amino acid positions in at least one modified FR that have a different amino acid are substituted with the amino acids in the corresponding positions of the selected subgroup consensus sequence.

19. (original) The method of claim 18, wherein the FR is a heavy chain FR1 and one of the amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and mixtures thereof.

20. (original) The method of claim 18 wherein amino acid positions 6 and 23 are substituted.

21. (original) The method of claim 19, wherein all of the amino acid positions at positions 1, 6, 11, 13, 18, 19, and 23 of the heavy chain FR1 are substituted.

22. (currently amended) The method of claim 1, wherein all of the amino acid positions in a FR that have a different amino acid are each substituted with the amino acid in the ~~correponding~~ corresponding FR position in the selected subgroup consensus sequence.

23. (original) The method of claim 22, wherein the FR is FR1, FR2, or FR3.

24. (currently amended) The method of claim 1, wherein all of the amino acid positions that have a different amino acid in all FR are each ~~subtituted~~ substituted with the amino acid in the ~~correponding~~ corresponding FR position in the selected subgroup consensus sequence.

25. (original) A method for preparing a humanized antibody or antigen binding fragment, comprising:

a) expressing a variable domain comprising at least one FR sequence from a selected human subgroup variable domain consensus sequence, and a HVR1 and/or HVR2 sequence of a non-human antibody in a host cell, wherein the selected human

subgroup consensus sequence is the human subgroup consensus sequence that has a HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the non-human antibody;

b) recovering the antibody variable domain from the host cell.

26. (original) The method according to claim 25, wherein the variable domain is a heavy chain variable domain.

27. (original) The method according to claim 25, wherein the variable domain is a light chain variable domain.

28. (currently amended) The method according to claim 26, wherein the HVR1 amino acid sequence of the variable domain of the antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14)[[,]] or GYDFTHYGMN (SEQ ID NO:18)~~, or GYSITSGYSWN (SEQ ID NO:19)~~.

29. (previously presented) The method according to claim 25, wherein the FR is selected form the group consisting of FR1, FR2, FR3, FR4 and mixtures thereof.

30. (original) The method according to claim 29, wherein the human subgroup FR consensus sequence is a heavy chain FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

31. (previously presented) The method of claim 25, wherein the variable domain comprises all of the FR of the selected human subgroup consensus sequence.

32. (previously presented) The method of claim 25, wherein the humanized antibody or antigen binding fragment has improved yield when produced in cell culture as compared to a or antigen binding fragment having the same HVR1 and/or HVR2 but without the selected FR.

33. (previously presented) The method of claim 25, wherein expressing comprises: expressing an expression vector comprising a polynucleotide encoding a variable domain comprising the HVR1 and/or HVR2 of the non-human antibody, and the selected FR.

34. (original) The method of claim 33, wherein the expression vector further comprises a polynucleotide encoding a constant domain connected to the polynucleotide encoding the variable domain to form a polynucleotide encoding a full-length heavy or light chain.

35. (currently amended) The method of claim 34, further comprising recovering ~~the full-length heavy or light chain or both from the culture~~

a) the full-length heavy chain;

b) the full-length light chain; or

c) the full-length heavy chain and the full-length light chain;

from the culture.

36. (previously presented) The method according claim 25, wherein the host cell is a prokaryotic host cell.

37. (previously presented) The method according to claim 25, wherein the host cell is a mammalian cell.

38. (currently amended) A method for improving the yield of an antibody or antigen binding fragment in cell culture, comprising:

expressing a heavy chain variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell,

wherein the at least one modified FR has a substitution of at least one amino acid position in at least one FR with a different amino acid, wherein

the at least one modified FR is formed by selecting a ~~the different amino acid is the amino acid found at the corresponding FR position of a~~ human heavy chain subgroup

variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a ~~corresponding~~ HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's heavy chain variable domain and substituting at least one amino acid position in at least one FR of the heavy chain variable domain of the antibody or antigen binding fragment with the different amino acid found at a corresponding position of the selected human heavy chain subgroup variable domain consensus FR sequence to form at least one modified FR region , wherein the antibody or antigen binding fragment with the modified FR of the heavy chain has improved yield in cell culture compared to an unmodified parent antibody or antigen binding fragment; and recovering the antibody or antigen binding fragment variable domain comprising the modified FR ~~framework~~ from the host cell.

39. (currently amended) A method for improving the yield of an antibody or antigen binding fragment in cell culture, comprising:

modifying ~~said~~ at least one FR sequence of a variable domain of the antibody or antigen binding fragment such that it is at least 50% identical in sequence to ~~the~~ a corresponding FR sequence of a selected subgroup consensus sequence to form a modified FR, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the different amino acid is the amino acid found at the corresponding FR position of the selected human subgroup variable domain consensus sequence, wherein the selected human subgroup consensus sequence has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 sequence of the variable domain, wherein the antibody or antigen binding fragment with the modified FR has improved yield in cell culture compared to an unmodified parent antibody or antigen binding fragment; and recovering the variable domain with the modified FR from the host cell.

40. (currently amended) The method according to claim 38, wherein the HVR1 amino acid sequence of the variable domain of the antibody or antigen binding fragment thereof

is GYTFTNYGIN (SEQ ID NO: 14)[[,]] or GYDFTHYGMN (SEQ ID NO: 18)~~, or GYSITSGYSWN (SEQ ID NO: 19)~~.

41. (previously presented) The method of claim 38, wherein at least two amino acid positions that have a different amino acid in at least one FR are substituted with amino acids in the corresponding position of the selected subgroup consensus sequence.

42. (original) The method of claim 41, wherein amino acid positions 6 and 23 of heavy chain FR1 are substituted.

43. (original) The method of claim 41, wherein amino acid positions 1, 6, 11, 13, 18, 19 and 23 of the heavy chain FR1 are substituted.

44. (original) The method according to any of claims 38, wherein expressing comprises expressing an expression vector comprising a first polynucleotide that encodes a variable domain comprising the HVR1 and/or HVR2 amino acid sequence of the antibody or antigen binding fragment and at least one modified FR.

45. (original) The method according to claim 44, wherein the expression vector further comprises a second polynucleotide encoding a constant domain, wherein the first and second polynucleotide are operably linked to a promoter; a heat stable enterotoxin sequence that can direct secretion to the periplasm; and a terminator sequence.

46. (previously presented) The method according to claim 38, wherein the host cell is a prokaryotic host cell.

47. (previously presented) The method according to claim 38, wherein the host cell is a mammalian cell.

48. (previously presented) The method according to claim 39, wherein the step of modifying comprises substituting all of the FRs of the variable domain with each of the corresponding FRs of the selected subgroup.

49. (previously presented) The method according to claim 38, wherein the framework region sequence is selected from the group consisting of FR1, FR2, FR3, FR4 and mixtures thereof.

50. (currently amended) A method for producing an antibody or antigen binding fragment in high yield from a host cell ~~in cell culture~~ comprising:

a) expressing a modified variable domain of the antibody or antigen binding fragment in ~~a~~ the host cell, wherein the modified variable domain has a substitution of at least one amino acid position proximal to a cys residue that participates in an intrachain variable domain disulfide bond with a different amino acid, wherein the different amino acid is ~~the~~ determined by selecting a ~~amino acid found at the corresponding FR position of a~~ human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a ~~corresponding~~ HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position proximal to the cys residue in the selected human subgroup variable domain consensus FR sequence having a different amino acid than that found at a corresponding position of the antibody or antigen binding fragment's variable domain, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified variable domain; , ~~wherein the antibody or antigen binding fragment comprising the modified variable domain has improved yield in cell culture compared to the antibody or antigen binding fragment~~; and

b) recovering the antibody or antigen binding fragment comprising the modified variable domain from the host cell.

51. (original) The method according to claim 50, wherein the variable domain is a heavy chain variable domain or a light chain variable domain.

52. (original) The method according to claim 51, wherein said at least one position is selected from the group consisting of the amino acid position 4 of the light chain, the amino acid position 6 of the light chain, the amino acid position 33 of the light chain, the amino acid position 35 of the light chain, the amino acid position 71 of the light chain and mixtures thereof.

53. (original) The method according to claim 51, wherein said at least one position is selected from the group consisting of the amino acid position 4 of the heavy chain, the amino acid position 6 of the heavy chain, the amino acid position 34 of the heavy chain, the amino acid position 36 of the heavy chain, the amino acid position 78 of the heavy chain, the amino acid position 104 of the heavy chain and mixtures thereof.

54. (original) The method according to claim 51, wherein said at least one position selected from the group consisting of amino acid position 4 of the light chain, amino acid position 6 of the light chain, amino acid position 33 of the light chain, amino acid position 35 of the light chain, amino acid position 71 of the light chain, and at least one position is selected from the group consisting of amino acid position 4 of the heavy chain, amino acid position 6 of the heavy chain, amino acid position 34 of the heavy chain, amino acid position 36 of the heavy chain, amino acid position 78 of the heavy chain, and amino acid position 104 of the heavy chain.

55. (previously presented) The method according to claim 50, wherein the at least one amino acid position is an amino acid position adjacent to the cys residue that forms an intra chain variable domain disulfide bond.

56. (original) The method according to claim 55, wherein the at least one amino acid position is selected from group consisting of amino acid position 21, amino acid position 22,

amino acid position 24, amino acid position 25, amino acid position 86, amino acid position 87, amino acid position 89 and amino acid position 90 in a light chain variable domain.

57. (original) The method according to claim 55, wherein the at least one amino acid position is selected from the group consisting of amino acid position 20, amino acid position 21, amino acid position 23, amino acid position 24, amino acid position 90, amino acid position 91, amino acid position 93 and amino acid position 94 in a heavy chain variable domain.

58. (currently amended) The method according to claim 50, wherein the variable domain is from an anti-VEGF antibody ~~or anti-IgE antibody~~.

59. (previously presented) The method according to claim 50, wherein the variable domain is from a humanized antibody or antigen binding fragment.

60. (previously presented) The method according to claim 50, wherein the step of expressing comprises expressing an expression vector comprising a first polynucleotide that encodes the modified variable domain sequence with an amino acid substitution in at least one of the amino acids proximal to a cys residue, wherein at least one amino acid is substituted with the amino acid at the corresponding position in the selected subgroup consensus sequence.

61. (currently amended) The method according to claim ~~50~~ 60, wherein the expression vector comprises a second polynucleotide encoding antibody constant region domains, wherein the first and second polynucleotide are operably linked to a promoter; a heat stable enterotoxin sequence that can directs secretion to the periplasm; and a terminator sequence.

62. (currently amended) The method according to claim 61, further comprising recovering ~~a full-length heavy or light chain or both~~

a) the full-length heavy chain;

b) the full-length light chain; or

c) the full-length heavy chain and the full-length light chain;

from the culture.

63. (currently amended) The method according to claim ~~60~~ 62, wherein the heavy chain variable domain has a substitution in amino acid position 4, 6, 34, 78, or mixtures thereof.

64. (currently amended) The method of claim ~~60~~ 62, wherein the light chain variable domain has a substitution in amino acid position 4, 71, or mixtures thereof.

65. (previously presented) The method according to claim 50, wherein the host cell is a prokaryotic host cell.

66. (previously presented) The method according to claim 50, wherein the host cell is a eukaryotic host cell.

67. (previously presented) The method according to claim 50, wherein the antibody or antigen binding fragment with modified variable domain has increased yield of at least 2 fold when produced in cell culture as compared to the antibody or antigen binding fragment.

68. (currently amended) The method according to claim 67, wherein the yield of the antibody or antigen binding fragment with the modified variable domain is ~~increasd~~ increased at least 2 to 16 fold as compared to the antibody or antigen binding fragment.

69. (original) The method of claim 50 further comprises:

a) identifying at least one amino acid position in a second variable domain of the antibody or antigen binding fragment that is proximal to a cys residue that forms an intrachain variable domain disulfide bond in the second variable domain;

b) selecting a variable domain subgroup consensus sequence having the most sequence identity with a HVR1 and/or HVR2 amino acid sequence of the second variable domain; and

c) determining whether the amino acid in the amino acid position identified in the second variable domain is different than the amino acid in the selected subgroup consensus sequence; and

d) placing at said at least one position in the second variable domain the amino acid found at the corresponding position in the selected subgroup consensus sequence to form a modified variable domain.

70. (original) The method of claim 69, wherein the variable domain is a heavy chain variable domain and the second variable domain is a light chain variable domain.

71. (original) A method for preparing a humanized antibody or antigen binding fragment, comprising:

a) expressing a variable domain in a host cell, wherein the variable domain is formed by substituting at least one amino acid position proximal to a cys residue that participates in an intrachain variable domain disulfide bond with a different amino acid, wherein the different amino acid is the amino acid found at corresponding position of a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 amino acid sequence of the variable domain; and

b) recovering the antibody variable domain from the host cell.

72. (original) The method according to claim 71, wherein the variable domain is a heavy chain variable domain.

73. (original) The method according to claim 71, wherein the variable domain is a light chain variable domain.

74. (currently amended) A method for improving the yield of an antibody or fragment thereof, comprising:

a) identifying at least one amino acid position in a heavy chain variable domain that is proximal to a cys residue that participates in an intrachain disulfide bond in the heavy chain variable domain;

b) selecting a first human antibody heavy chain variable domain subgroup consensus sequence having the most identity with a HVR1 and/or HVR2 amino acid sequence of the heavy chain variable domain; and

c) placing at said at least one position in the heavy chain variable domain an amino acid found at the corresponding position in the selected first subgroup;

d) identifying at one amino acid position in a light chain variable domain that is proximal to a cys residue that participates in an intrachain disulfide bond in the light variable domain;

e) selecting a second human antibody light chain variable domain subgroup consensus sequence having the most sequence identity with a HVR1 and/or HVR2 amino acid sequence of the light chain variable domain; ~~and~~

f) placing at said at least one position in the light chain variable domain an amino acid found at the corresponding position in the second selected subgroup; and

g) expressing said antibody or antibody fragment thereof.

75-81. (cancelled)

82. (original) A method for improving the yield of antibody or antigen binding fragments in cell culture, comprising:

expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell, wherein the modified FR is obtained by substituting at least one amino acid in a least one FR of a parent variable domain of the antibody or antigen binding fragment with a different amino acid, wherein the different amino acid is an amino acid found at the corresponding FR position of a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 amino acid sequence of the parent variable domain to form a modified FR, wherein antibody or antigen binding fragment comprising the

modified FR has improved yield in cell culture compared to the parent antibody or antigen binding fragment; and recovering the antibody or antigen binding fragment comprising at least one modified FR from the host cell.

83. (original) The method according to claim 82, wherein the parent variable domain is obtained from an antibody is selected from the group consisting of a humanized antibody, a monoclonal antibody, a human antibody, a multispecific antibody, diabodies, or an antibody generated by phage display.

84. (currently amended) The method according to claim 83, wherein the parent variable domain is from an antigen binding fragment that is a Fab fragment, ~~F(ab')2~~ F(ab')$_2$ fragment, scFV fragment, or ~~sc(Fv)2~~ sc(Fv)$_2$ fragment, a single arm antibody or single chain antibody.

85. (currently amended) The method according to claim 82, wherein the parent antibody variable domain is from an anti-VEGF antibody ~~or anti-IgE antibodies~~.

86. (previously presented) The method according to claim 82, wherein the parent antibody variable domain is from a humanized antibody.

87. (previously presented) The method according to claim 82, wherein expressing comprises expressing an expression vector comprising a first polynucleotide that encodes the variable domain comprising the HVR1 and/or HVR2 amino acid sequence and the modified FR.

88. (currently amended) The method according to claim 82, wherein the HVR1 amino acid sequence of the variable domain of the antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14)[[,]] or GYDFTHYGMN (SEQ ID NO: 18~~, or GYSITSGYSWN (SEQ ID NO: 19)~~.

89. (previously presented) The method according claim 82, wherein the host cell is a prokaryotic host cell.

90. (currently amended) The method according to claim 82, wherein the variable domain is a) a heavy chain variable domain, b) ~~or~~ light chain variable domain, or c) a heavy chain variable domain and a light chain variable domain ~~both~~.

91. (previously presented) The method according to claim 82, wherein the host cell is a mammalian cell.

92. (previously presented) The method according to claim 82, wherein the FR is selected from the group consisting of FR1, FR2, FR3, FR4 and mixtures thereof.

93. (previously presented) The method according to claim 82, wherein the human subgroup FR consensus sequence is a FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

94. (previously presented) The method according to claim 82, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold compared to the antibody or antigen binding fragment with the parent variable domain.

95. (original) The method according to any of claims 94, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold to 16 fold.

96. (original) A method for improving the yield of antibody or antigen binding fragments in cell culture, comprising:

a) expressing a polynucleotide encoding a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell, wherein the modified FR has a substitution of at least one amino acid in the at least one FR with a different amino acid, wherein the different amino acid is the amino acid found at the

corresponding FR position of a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 sequence of the variable domain, wherein the antibody or antigen binding fragment comprising the variable domain with the modified FR has improved yield in cell culture compared to an antibody or antigen binding fragment with an unmodified variable domain; and

b) recovering the antibody or antigen binding fragment comprising the modified FR from the host cell.

97. (original) The method according to claim 96, wherein the polynucleotide is an expression vector that comprises a polynucleotide encoding a variable domain comprising the modified FR and at least one constant region domain operably linked to a promoter, a heat stable enterotoxin sequence that can direct secretion to the periplasm, and a terminator sequence.

98. (previously presented) The method according to claim 96, wherein the host cell is a prokaryotic host cell.

99. (previously presented) The method according to claim 96, wherein the host cell is a eukaryotic host cell.

100. (original) A method for improving the yield of antibody or antigen binding fragments in cell culture, comprising:

expressing a polynucleotide molecule encoding a modified variable domain of a parent antibody or antigen binding fragment in a host cell, wherein the modified variable domain has a substitution of at least one amino acid proximal to a cys reside that participates in an intrachain variable domain disulfide bond with a different amino acid, wherein the different amino acid is the amino acid found at corresponding position of a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a corresponding HVR1 and/or HVR2 amino acid sequence of the parent variable domain, wherein the antibody or

antigen binding fragment comprising the modified variable domain has improved yield in cell culture compared to the parent antibody or antigen binding fragment; and

recovering the antibody or antigen binding fragment comprising the modified variable domain from the host cell.

101. (currently amended) The method according to claim 100, wherein the polynucleotide molecule ~~comprises~~ is comprised within an expression vector that comprises a polynucleotide molecule encoding the modified variable domain and at least one constant region domain operably linked to a promoter, a heat stable enterotoxin sequence that can direct secretion to the periplasm, and a terminator sequence.

102. (previously presented) The method according to claim 100, wherein the host cell is a prokaryotic host cell.

103. (previously presented) The method according to claim 100, wherein the host cell is a eukaryotic host cell.

104. (original) A method for improving the yield of antibody or antigen binding fragments in cell culture, comprising:

a) comparing a HVR1 and/or HVR2 amino acid sequence of a variable domain of a parent antibody or antigen binding fragment to a corresponding HVR1 and/or HVR2 amino acid sequence of each human subgroup variable domain consensus sequences and selecting a human subgroup variable domain consensus sequence that has the most sequence identity with the HVR1 and/or HVR2 sequence of the variable domain;

b) identifying at least one amino acid position in at least one FR in the variable domain selected from the group consisting of FR1, FR2, FR3 , FR4 and mixtures thereof, wherein the amino acid position has a different amino acid than the amino acid at a corresponding position of the selected human subgroup variable domain consensus sequence; and

c) substituting the at least one amino acid position identified in step (b) with the amino acid in the corresponding position of the selected human subgroup variable domain consensus sequence to form a variable domain with a modified FR;

wherein the antibody or antigen binding fragment with the modified FR has improved yield in cell culture compared to the parent antibody or antigen binding fragment.

105. (original) The method according to claim 104, wherein the parent antibody is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a human antibody, a multispecific antibody, diabodies, or an antibody generated by phage display.

106. (currently amended) The method according to claim 105, wherein the parent antigen binding fragment is a Fab fragment, ~~F(ab')2~~ $F(ab')_2$ fragment, scFV fragment, or ~~sc(Fv)2~~ $sc(Fv)_2$ fragment, single arm antibody, or single chain antibody.

107. (currently amended) The method according to claim 104, wherein the parent antibody is an anti-VEGF antibody ~~or an anti-IgE antibody~~.

108. (original) The method according to claim 107, wherein the parent antibody is a humanized antibody.

109. (previously presented) The method of claim 104, wherein step (c) comprises modifying a polynucleotide encoding the parent variable domain to form a polynucleotide encoding a variable domain with a modified FR, wherein the modified FR has at least one amino acid position substituted with the amino acid in the corresponding position of the selected human subgroup variable domain consensus sequence.

110. (original) The method of claim 109, wherein the polynucleotide further comprises a polynucleotide encoding a constant region domain connected to the polynucleotide

encoding the variable domain with modified FR parent to form a polynucleotide encoding a full-length heavy or light chain.

111. (currently amended) The method of claim ~~110~~ 109, wherein the polynucleotide ~~further comprises~~ is comprised within an expression vector.

112. (original) The method of claim 111, further comprising culturing a host cell comprising the expression vector; and recovering a full-length heavy or light chain or both from the culture.

113. (original) The method according to claim 112, wherein the host cell is a prokaryotic host cell.

114. (original) The method according to claim 112, wherein the host cell is a mammalian cell.

115. (previously presented) The method according to claim 104, wherein the variable domain is a heavy chain variable domain or a light chain variable domain.

116. (currently amended) The method according to claim 115, wherein the HVR1 amino acid sequence is GYTFTNYGIN (SEQ ID NO: 14)[[,]] or GYDFTHYGMN (SEQ ID NO:18)~~, or GYSITSGYSWN (SEQ ID NO:19)~~.

117. (previously presented) The method according to claim 104, wherein the framework region is selected from the group consisting of FR1, FR2, FR3, FR4, and mixtures thereof.

118. (original) The method according to claim 117, wherein the human subgroup FR consensus sequence is a heavy chain FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

119. (previously presented) The method according to claim 104, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold compared to the parent antibody or antigen binding fragment.

120. (original) The method according to claim 119, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold to 16 fold compared to the parent antibody or antigen binding fragment.

121. (previously presented) The method of claim 104, wherein at least two identified amino acid positions in at least one FR are substituted with amino acids in the corresponding position of the selected subgroup consensus sequence.

122. (currently amended) The method of ~~claim121~~ claim 121, wherein the FR is a heavy chain FR1 and one of the identified amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and mixtures thereof.

123. (original) The method of claim 122 wherein amino acid positions 6 and 23 are substituted.

124. (original) The method of claim 122, wherein all of the amino acid positions at position, 1,6,11,13,18,19, and 23 of the heavy chain FR1 are substituted.

125. (currently amended) The method of claim 104, wherein all of the identified amino acid positions in a FR are each substituted with the amino acid in the ~~correponding~~ corresponding position in the selected subgroup consensus sequence.

126. (original) The method of claim 125, wherein the FR is FR1, FR2, or FR3.

127. (currently amended) The method of claim 104, wherein all of the identified amino acid positions in all FR are each ~~subtituted~~ substituted with the amino acid in the ~~correponding~~ corresponding position in the selected subgroup consensus sequence.

128. (cancelled)